



How do non-specific mechanisms of toxicity fit into the AOP framework? The example of narcosis

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University of Antwerp / Zebrafishlab Dept Veterinary Sciences; S. Nørgaard Schmidt, Technical University of Denmark / Dept Environmental Engineering; W. Maho, University of Antwerp / Toxicological Centre Dept Pharmaceutical Sciences; P. Mayer, Technical University of Denmark / Department of Environmental Engineering; A. Covaci, University of Antwerp / Toxicological Centre Dept of Pharmaceutical Sciences; L. Vergauwen, University of Antwerp / Zebrafishlab Dept Veterinary Sciences. Adverse Outcome Pathway (AOP) development is currently being formalized around a set of internationally harmonized principles. While these principles can often be applied in a relatively straightforward manner in cases in which the sequence of key events (KEs) is fairly specific, defining and describing appropriate re-usable KEs can be particularly challenging when relatively non-specific toxicological mechanisms are involved. A well-known example of such a non-specific mechanism is membrane disruption through narcosis, which is commonly accepted to result from accumulation of lipophilic chemicals in membranes disrupting membrane integrity and function. It has been difficult to delineate a complete AOP for narcosis, resulting in insufficient understanding of the exact mechanisms involved to e.g. support robust read across groupings based on mechanism of action. We summarized the two main pathways that have been described for narcosis in a hypothesized AOP. The first outlines a generalized pathway leading to a loss of equilibrium and mortality at the organismal level through changes in cellular respiration and metabolic rate. The second focused on disruption of epithelium of primary and secondary gill lamellae resulting in pathologic alterations, ultimately causing hypoxia and respiratory failure. We applied a passive dosing method to expose zebrafish embryos up to 5 days to a linear dilution series of phenanthrene. We observed reduced survival (LC₅₀: 310.0 µg/l), and reduced growth with increasing accumulated dose.⁵⁰ We observed that the distance travelled was significantly reduced in all phenanthrene exposure concentrations. We found that while exposed larvae were able to reach high swim speeds (> 10 mm/s), they travelled less distance at these high speeds. We also found that impaired inflation of the posterior swim bladder chamber was the most important sublethal morphological effect after phenanthrene exposure. One could expect that the reduced swimming activity is caused by the failure to inflate the swim bladder. However, the effect of impaired swim bladder inflation on swimming activity was small relative to the narcosis effect. Currently, we are defining underlying key events leading to these adverse outcomes. We are currently in the process of determining the distribution of narcotic compounds across different membrane types (cell membrane versus mitochondrial membrane), and of evaluating *in vitro* tools for the assessment of narcotic effects.